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Future pharmacotherapy for post-traumatic stress disorder: Prevention and treatment

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In the future, medications for post-traumatic stress disorder (PTSD) will be designed and selected to combat the unique pattern of psychobiological abnormalities associated with this disorder. That will be a radical departure from the present empirical approach in which clinical trials are conducted with medications initially developed as antidepressants, anxiolytics, and anticonvulsants.

In the future, PTSD will be understood from a longitudinal perspective as a psychobiological abnormality that evolves through different stages over time. As with other medical disorders, such an approach will inform treatment decisions, as different medications will be more effective for different stages of the disorder.

In the future, it will be understood that some traumatized people are more resilient, while others are more vulnerable to developing PTSD. The understanding of key differences in the psychobiological profile of resilient versus vulnerable individuals will guide pharmacological strategies for the prevention of PTSD.

Two ground rules will guide the comments to follow. First, to look toward a future approach to pharmacotherapy dominated by rational rather than empirical priorities, as noted above. Second, to emphasize preventive public health strategies rather than tertiary, end-stage treatment approaches, as at present. Therefore, we start with a consideration of the psychobiology of the human stress response and what we have learned about the pathophysiology of PTSD. Using this information, we will speculate on future pharmacological methods to foster resilience against, prevention of, and acute interventions for PTSD and other pathological responses to

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traumatic stress. Finally, we will consider new approaches for treatment of chronic PTSD.

The human stress response and the pathophysiology of PTSD

The human stress system has evolved for coping, adaptation, and preservation of the species. It encompasses central and peripheral nervous systems, the endocrine system, and the immunological system. Its two major components are the hypothalamic-pituitary-adrenocortical (HPA) and the locus coeruleus/norepinephrine-sympathetic (LC/NE) systems. Corticotropin releasing factor (CRF) is the ignition switch for the human stress response which not only activates HPA, LC/NE, and immunological mechanisms, but a complex cascade of reactions mediated by many other neurotransmitter, neurohormonal, immunological and metabolic mechanisms including: adrenergic, serotonergic, opioid, glutamatergic, gabergic, cholinergic, and cytokine systems [1,2]. (It is important to keep in mind that CRF may also initiate more fine-grained actions involving only the HPA, only the LC/NE, or only other specific immunological or neurobiological systems. In the face of an overwhelming stressor, however, it is not unreasonable to consider CRF from the present standpoint, as the prime mover in the complex spectrum of actions that characterize the human stress response.)

PTSD results when a traumatic experience overwhelms the capacity of an individual's stress system. Failure to cope with the demands of traumatic stress might take a number of forms such as inability to mobilize an adequate response, inability to achieve normal recovery, and inability to calibrate the magnitude of the stress response to the actual psychobiological demands of the traumatic situation.

In short, PTSD exemplifies the human stress response gone wrong. As a result of the organism's failure to cope and recover, key psychobiological functions are altered. Dysregulation of HPA, LC/NE, and immune mechanisms produces many secondary abnormalities that are mediated through a cascade of downstream mechanisms. In chronic PTSD, a new balance is achieved in the face of such stable psychobiological alterations. Countermeasures are brought into play to compensate for: (1) the failure to mount an adequate response, (2) the failure to shut off activated mechanisms in order to achieve normal recovery, (3) the failure to habituate to repeated challenges of the same kind, and (4) the failure to calibrate subsequent stress system responses to realistic demands of the situation. There are also anatomic consequences of altered stress system function, including atrophy of brain regions such as the hippocampus. McEwen [2] has called the process of achieving stability in the face of such altered neurobiological mechanisms, allostasis; the price of achieving such stability in the face of these deleterious functional alterations is called allostatic load. Allostatic load in chronic PTSD has already been detected in a number of key systems shown in Table 1 such as: HPA, LC/NE, serotonergic, opioid, and serotonergic systems. It is reasonable to expect

Table 1
Treatment of PTSD

Neurobiological system	Proposed abnormality	Proposed treatment
CRF	Increased CRF	CRF antagonists, NPY agonists, opioid agents
HPA	GR supersensitivity Variable cortisol levels	Glucocorticoids (cortisol), DHEA, SSRIs
Adrenergic	LC/NE hyperactivity Enhanced LC/NE activity at baseline Blunted NPY activity	NPY agonists, opioid agents, CRF antagonists, antiadrenergic agents (α_2 agonists, β antagonists, α_1 antagonists)
Serotonergic	Systemic dysregulation	SSRIs, nefazadone, more selective 5-HT agents
Opioid	Systemic dysregulation	Selective opioid agents or antagonists
Substance P	Enhanced activation?	Substance P antagonists
Glutamatergic	Impaired glutamatergic synaptic function	Modulators of NMDA, non-NMDA, and metabotropic glutamate receptors
Limbic/cortical neuronal excitability	Sensitization/kindling	Anticonvulsants
Dendritic/neuronal degeneration	Hippocampal atrophy	Neurogenesis promoters: antidepressants, 5-HT_{1A} agonists, IGF-1 agonists

Abbreviations: PTSD, post-traumatic stress disorder; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenocortical; GR, glucocorticoid receptor; LC/NE, locus coeruleus/norepinephrine-sympathetic; NPY, neuropeptide Y; DHEA, dehydroepiandrosterone; SSRIs, selective serotonin reuptake inhibitors; NMDA, N-methyl-D-aspartate; IGF-1, insulin-like growth factor-1.

that future research will detect allostatic load in glutamatergic, gabergic, and immunological mechanisms as well. More information on such abnormalities can be found elsewhere [3,4,5] and in this article.

Allostatic load signifies adverse changes in neurobiological function. If there can be a change for the worse, however, then there might also be a change for the better. Indeed, allostasis in a positive direction would be expected to be salutogenic and buffer the potentially deleterious impact of allostatic load. We refer to such salutary changes as allostatic support [6]. Resilience against, prevention of, and treatment for PTSD can all be understood in terms of allostatic support.

Resilience and prevention: general principles

Individuals differ in their likelihood of developing PTSD following exposure to traumatic stress. Epidemiological research suggests that most

traumatized people do not develop PTSD, even after surviving the most terrifying and dehumanizing interpersonal violence, such as rape, torture, and military combat [7]. There is growing evidence that a number of important risk factors affect resilience or vulnerability to PTSD, such as genetic endowment, childhood development, the history of abuse and/or neglect, education, trauma severity, and the post-traumatic recovery environment [8]. It has been suggested that psychophysiological factors such as reactivity, conditionability, resistance to extinction/habituation [9,10], and different personality configurations [11] also may constitute risk factors for PTSD.

From a psychobiological perspective, it seems reasonable to operationalize resilience and vulnerability in terms of the stress system's coping capacity. Resilient individuals are those who are abnormally equipped to: (1) mobilize CRF-activated HPA, LC/NE, immunological, and all other downstream neurobiological mechanisms in the face of extreme or traumatic stress, and (2) shut off such activation when the stress response is no longer needed. Vulnerable individuals, on the other hand, are those whose stress response is inadequate or whose recovery is delayed after CRF activation of HPA, LC/NE, and other mechanisms [2,12,13].

Any intervention that bolsters resilience is prevention. Pharmacological strategies to prevent PTSD might be developed to fortify the stress system in people with functional deficits in a key component of their stress system such as inadequate or excessive CRF mobilization.

Preventive pharmacotherapy for PTSD would begin with a psychobiological assessment protocol that would focus on the primary components of the stress response rather than downstream mechanisms. It might be a two-stage process measuring both baseline and elicited stress system measures. The first stage, analogous to a serum lipid profile for detecting individuals at greatest risk for atherosclerosis, might consist of baseline serum or urinary indicators of HPA, LC/NE, opioid, and immunological function (Table 2). Abnormal levels of any of these stress system components might identify those individuals most vulnerable (or resilient) to developing PTSD following traumatization. Seeman et al. [14] have used such a baseline battery to correctly identify individuals at greatest risk of exhibiting adverse health consequences from chronic stress (e.g., allostatic load).

Because the hallmark of PTSD is hyperreactivity, the second stage of stress system assessment might be a series of provocative tests to probe the coping capacity of the stress system itself. This would be analogous to a treadmill test to detect heart disease or a glucose tolerance test to detect diabetes mellitus in medical practice. Such provocative tests (shown in Table 2) might include: (1) startle paradigms to assess physiological reactivity, conditionability, and resistance to extinction, (2) in vivo stress paradigms to assess mobilization of HPA, LC/NE, opioid, and immunological components of the stress response, (3) dexamethasone suppression test to assess glucocorticoid receptor sensitivity, (4) yohimbine provocation to assess LC/NE function, or (5) provocation to assess humoral or cell-mediated immunity. Should abnormalities

Table 2
Fostering resilience/prevention of PTSD

Step		
1 Baseline assessment	HPA function	CRF, ACTH, cortisol, DHEA
	LC/NE function	Norepinephrine, epinephrine, dopamine, MHPG
	Other	NPY, opioids, cytokines, substance P
2 Provocative tests	Physiological protocols	Hyperreactivity, conditionability, resistance to extinction
	In vivo stress paradigms to assess mobilization of	HPA, LC/NE, other function (per Step 1)
	dexamethasone suppression	Glucocorticoid receptor sensitivity
	Yohimbine provocation	LC/NE and NPY response
	Immunological provocation	Humoral and cell-mediated immunity
3 Periodically repeat Steps 1 and 2 for:		People exposed to traumatic stress
		People in high-risk professions

Abbreviations: PTSD, post-traumatic stress disorder; HPA, hypothalamic-pituitary-adrenocortical; LC/NE, locus coeruleus/norepinephrine-sympathetic; CRF, Corticotropin releasing factor; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; NPY, neuropeptide Y; MHPG, 3-methoxy-4-hydroxyphenylglycol.

Treatment: Correct abnormalities detected in Steps 1, 2, or 3.

be detected either at baseline or following provocation, the next question would be whether they can be corrected with pharmacological and/or behavioral treatment. Some possible medication treatment options include: CRF antagonists, dehydroepiandrosterone (DHEA), antiadrenergic agents, neuropeptide Y (NPY) enhancers, opioid modulators, and agents normalizing immunological responses.

Thus, we have outlined a prophylactic strategy to promote resilience and prevent PTSD that uses psychobiological tools to detect vulnerable individuals and that uses pharmacological (and behavioral) interventions to correct such deficiencies.

Recent research with US Special Forces military personnel provides a concrete example of this approach. Morgan et al. [15,16] monitored the stress response among military personnel exposed to an extremely stressful training experience at Fort Bragg, NC. They showed that individuals who were best able to mobilize NPY tolerated the experience and performed better than those unable to achieve comparable NPY levels. These results suggest that stress-induced NPY mobilization may be an important index of resilience against PTSD. It also suggests that pretreatment with an NPY agonist might be an effective prophylactic strategy to prevent PTSD among people in dangerous professions who are unable to mobilize sufficient endogenous NPY levels on their own.

Resilience and prevention for previously traumatized individuals

The previous discussion focused on a preventive strategy for people who have never been exposed to traumatic stress. What should be done for people who have had or probably will have such exposure? It was shown (prior to September 11, 2001) that in the United States, a nation that had not seen a war on its own soil since 1865, over half of all adult American men and women had been exposed to at least one traumatic event during the course of their lives [7]. In nations in which conflicts have or continue to rage within recent memory, the lifetime prevalence of exposure to traumatic events among adults is much higher: 91.9% in Algeria, 78.0% in Ethiopia, and 74.4% in Cambodia [17]. It is also known that there are a number of professions in which individuals are routinely exposed to potentially traumatic events in the course of their normal duties; these include soldiers, police, firefighters, emergency medical personnel, and disaster/refugee mental health clinicians. Thus, we must periodically repeat the baseline assessments and provocative tests (e.g., Steps 1 and 2 in Table 2) for people who have been exposed to traumatic stress and for those in high risk professions because they are at greater risk to develop PTSD.

A recent experiment suggests that trauma exposure itself may produce psychobiological abnormalities even among people who do not develop PTSD. Heim et al. [18] tested the adrenocorticotropic hormone (ACTH) response to CRF among three groups of women: those with a history of childhood sexual abuse (CSA) and depression; those with CSA and no depression, and a control group with neither CSA nor depression. The CSA/depressed group (all but one of whom also had PTSD) showed a blunted ACTH response in comparison to controls. In contrast, the CSA/no-depression (and mostly no-PTSD) group exhibited a significantly greater ACTH response to CRF than the controls. In other words, the traumatic stress of CSA produced opposite HPA abnormalities depending on whether the women had depression or not. The implications for PTSD prevention are that: (1) it may be especially important to foster resilience and bolster allostatic support for trauma exposed/non-PTSD individuals, and (2) the specific prophylactic pharmacotherapy required for such individuals may be different from what is needed for never-traumatized individuals.

Treatment of acute stress responses: is there a morning after pill?

During the normal human stress response, CRF rapidly mobilizes HPA and LC/NE mechanisms. After the traumatized individual's requirements for such activation have passed, recovery of normal function is mediated, in part, through glucocorticoids, NPY, and opioids. It is possible that individuals most likely to develop PTSD are: (1) those who produce the most intense HPA and/or LC/NE activation, (2) those who are unable to achieve normal recovery because of blunted glucocorticoid, NPY and/or opioid mobilization, or (3) a combination of both factors.

Most of these speculations are extrapolations from findings with chronic PTSD (Table 1) showing enhanced HPA function (indicated by elevated CRF and increased glucocorticoid receptor sensitivity) as well as enhanced LC/NE function (indicated by adrenergic hyperreactivity, yohimbine sensitivity, elevated 24-hour urine catecholamine, and downregulation of adrenergic receptors). Evidence for inadequate countermeasures to shut off the stress response is less robust but includes reduced glucocorticoid levels [19], blunted NPY levels [16,20], and reduced opioid levels [21] among individuals with PTSD.

The few studies on acutely traumatized individuals are generally consistent with these findings. Emergency room patients with enhanced post-traumatic heart rates were more likely to develop PTSD than those with lower cardiovascular activation [22,23]. Furthermore, emergency room patients with lower cortisol levels were also most likely to develop PTSD [24,25].

Therefore, future pharmacological treatment for acutely traumatized individuals will seek to reduce the magnitude of the stress response and to promote rapid recovery of normal function. As shown in Table 1, this might be accomplished by: (1) reducing CRF activity with CRF-antagonists, NPY agonists, or opioid agents, (2) reducing HPA activation with glucocorticoids (such as cortisol) or with an adrenal steroid such as DHEA, or (3) reducing LC/NE activation with NPY agonists and/or a variety of antiadrenergic agents (such as clonidine/guanfacine, propranolol, or prazosin).

Rapid antagonism of CRF would seem to be the most direct approach because it would reduce enhanced HPA, LC/NE, immunological, and secondary stress responses. Rapid reduction of post-traumatic HPA activation with cortisol (or other glucocorticoids) might prevent subsequent sensitization of glucocorticoid receptors, thereby preventing the development of glucocorticoid receptor supersensitivity. Indeed, treatment of septic shock patients with intravenous doses of the glucocorticoid, hydrocortisone, reduced the incidence of PTSD in comparison with patients who did not receive such treatment [26]. Finally, rapid antagonism of LC/NE activity with NPY agonists or antiadrenergic agents might not only prevent elevations in heart rate shown to predict PTSD [22,23] but would also be expected to prevent adrenergically mediated encoding of traumatic memories [27].

As more psychobiological research is carried out with acutely traumatized individuals, other pharmacological strategies will undoubtedly become apparent. In short, it does appear that the search for a "morning after pill" to prevent PTSD is likely to produce clinically useful results.

Treatment of chronic PTSD

The best treatment for PTSD is to abolish trauma in the first place by preventing war, rape, child abuse, torture, industrial accidents, etc. The next best approach is to foster resilience and bolster allostatic support so that individuals have optimized their coping capacity prior to exposure to traumatic stress. The third best option is early detection and treatment of acutely

traumatized individuals to prevent a prolonged stress response that may produce abnormalities in HPA, LC/NE, immunological, and downstream mechanisms. When all such measures have either failed or not been initiated soon enough, the clinical challenge becomes the treatment of chronic PTSD.

Whereas the emphasis in prevention and acute intervention focuses exclusively on primary components of the human stress response (e.g., CRF, HPA, LC/NE, and probably immunological mechanisms) the focus in chronic PTSD may include downstream mechanisms. It may be on secondary neurotransmitter (e.g., 5-HT, dopamine, gabergic, N-methyl-D-aspartate [NMDA], substance P), hormonal (e.g., thyroid, gonadotropic, growth hormone), metabolic (Metabolic Syndrome X) or even neuronal consequences (e.g., sensitization, degeneration/atrophy). Furthermore, it is possible that PTSD is an evolving process that progresses through a sequence of stages in which the most severe stages are the least responsive to treatment [28,29]. End-stage PTSD may be a state marked by extreme hyperreactivity, hypervigilance, stress intolerance, cognitive disruption, and hippocampal atrophy.

Treatment goals for chronic PTSD may be very different than for more acute stages in the process. As discussed previously, treatment for acute post-traumatic reactions seeks to normalize the primary components of the human stress response (e.g., CRF, HPA, and LC/NE function), thereby preventing the development of PTSD. Treatment for recent onset PTSD seeks to eliminate symptoms of the disorder itself in order to achieve complete remission of reexperiencing, avoidant/numbing, or hyperarousal symptoms. In contrast, treatment of chronic PTSD might focus on a late-stage abnormality rather than the DSM-IV symptoms of PTSD. For example, hippocampal atrophy caused by dendritic and neuronal degeneration might be considered the major priority for treatment where the goal is to arrest the neurodegenerative process and, hopefully, improve cognitive function. As with any other chronic medical or psychiatric disorder, when it is too late to strive for complete remission, clinical interventions must try to optimize functional capacity and to prevent further deterioration.

Table 1 combines empirical findings with educated guesses about the spectrum of psychobiological alterations associated with chronic PTSD. It also proposes treatments (some of which are yet to be developed) to ameliorate such abnormalities. The number of neurobiological systems exhibiting PTSD-related abnormalities attests to the cumulative allostatic load from so many pathophysiological changes and illustrates why PTSD is such a complex chronic disorder characterized by deterioration in physiological, emotional, cognitive, and behavioral function.

Increased CRF activity and HPA dysregulation

Although we have emphasized reduction of CRF activity and normalization of HPA function as a major priority in preventive and acute interventions, it is not at all clear how much benefit might be gained from such

measures in chronic PTSD. Clinical trials with CRF antagonists will certainly be conducted as soon as the pharmaceutical industry has developed agents safe enough to administer to humans. PTSD symptoms that might respond to such treatment include anxiety, hyperarousal, depression, and stress intolerance [30]. Yehuda [19] has suggested that HPA dysregulation, especially with regard to glucocorticoid receptor supersensitivity may contribute significantly to hippocampal atrophy. Friedman and McEwen [6] have suggested that sustained HPA dysregulation in chronic PTSD may be a major factor in the increased vulnerability to medical disorders that appears to be associated with PTSD. Clearly, normalization of HPA function will be an important focus for clinical trials in both acute and chronic PTSD. As suggested previously, there are a number of pharmacological agents, in addition to CRF antagonists, that might be effective in this regard such as NPY agonists, opioid agents, selective serotonin reuptake inhibitors (SSRIs), and adrenal sterioids such as DHEA.

LC/NE system

As with the HPA system, preventive or acute intervention with antiadrenergic agents or NPY agonists has been emphasized previously. Treatment with such agents would be expected to reduce hyperreactivity, hyperarousal, hypervigilance, and panic/anxiety. Because adrenergic agonists enhance encoding of traumatic memories [27], antiadrenergic agents might ameliorate reexperiencing symptoms such as intrusive recollections, traumatic nightmares, PTSD flashbacks, and psychological/physiological distress triggered by trauma-related stimuli. Finally, as yohimbine can elicit dissociative episodes, antiadrenergic agents and NPY agonists may be especially effective treatment for dissociation [16,20,30].

Serotonergic system

The serotonergic system has important reciprocal relationships with both the HPA and LC/NE systems. Excessive HPA activity associated with chronic PTSD produces downregulation of 5-HT_{1A} receptors and upregulation of 5-HT_2 receptors, resulting in abnormal neurotransmission in key limbic nuclei [31,32]. Clinical studies have shown that PTSD patients exhibit a number of abnormalities associated with low 5-HT such as impulsivity, rage, aggression, depression, panic, obsessional thoughts, and chemical dependency [33].

The first two drugs to receive US Federal Drug Administration approval as indicated treatments for PTSD are the SSRI antidepressants sertraline and paroxetine. Among their other actions, SSRIs produce amelioration in all three symptom clusters of PTSD. Other antidepressants that affect serotonergic function such as nefazadone and amitriptyline have also shown efficacy in PTSD. Given the complexity of the serotonergic system with its large

number of distinctive receptor types, it can be expected that in the future, greater efficacy may be achieved with more selective serotonergic agents (such as postsynaptic 5-HT_{1A} agonists), especially in chronic PTSD.

Finally, post-synaptic 5-HT_{1A} receptors found in astrocytes and other glia appear to promote neurogenesis of limbic nuclei [34]. This may be another important reason why serotonergic agents will continue to play an important role in the treatment of chronic PTSD. The merging importance of neurogenesis in pharmacotherapy for PTSD will be discussed subsequently.

Opioid systems

Stress-induced opioid activity produces inhibition of both HPA and LC/NE systems, thereby promoting recovery. This system is also dysregulated in PTSD, with a number of reports showing abnormal beta-endorphin and methionine enkephalin levels [2,35] as well as lower pain thresholds among individuals with PTSD [36]. Therapeutic trials with opioid agents have scarcely begun. There is particular interest in the possibility that an opioid antagonist, such as naltrexone, may have unique applicability as treatment for PTSD patients with comorbid alcohol or substance abuse/dependency [37].

Substance P

Based on their neuroanatomic distribution, it appears likely that substance P neurons are activated during the human stress response and have reciprocal interactions with the LC/NE system. Safe substance P antagonists have been synthesized and, in one randomized trial, the substance P antagonist MK-869 was as effective an antidepressant as the SSRI, paroxetine [38]. Research with this class of medications certainly seems to offer possibilities for important clinical and conceptual advances in PTSD.

Glutamatergic systems

Glutamatergic mechanisms are key to neuronal activation and to cognitive functions such as perception, appraisal, conditioning, extinction, and memory. Fear conditioning, sensitization, and resistance to extinction, all of which are mediated at NMDA synapses, are altered in PTSD [39]. Information processing is disrupted with respect to learning and cognition. Memory function may be altered in the direction of excessive recall (e.g., intrusive recollections) or problems with retrieval (e.g., amnesia). Finally, dissociation, an abnormality that is beginning to be understood as a very important post-traumatic symptom, appears to represent a disruption of glutamatergic function [40,41]. It appears likely that medication normalizing neurotransmission at NMDA, non-NMDA, and metabotropic glutamate receptors may produce benefits for individuals with chronic PTSD.

Limbic/cortical neuronal excitability

Post et al. [28,29] have proposed that progressive increases in neuronal excitability of key limbic nuclei may be an underlying mechanism for the evolution of intrusive recollections. In early stages, there is a lowering of excitatory thresholds to stimulation by trauma-related stimuli. As the process continues, however, such neurons may fire on their own (without being triggered by external trauma cues) and produce spontaneous intrusive recollections, traumatic nightmares, PTSD flashbacks, and arousal symptoms such as hyperarousal, irritability, startle, and hypervigilance. This model of neuronal sensitization/kindling suggests that anticonvulsants may have a unique role in treatment of chronic PTSD, especially when spontaneous neuroexcitability has evolved. Unfortunately, promising earlier open label trials with the anticonvulsants carbamazepine and valproate have not led to randomized trials either with these medications or with newer anticonvulsants such as lamotrigine and gabapentin.

Dendritic/neuronal degeneration

Structural brain imaging has suggested that hippocampal volume may be reduced in PTSD patients [42,43]. This reduction in volume may be caused by stress-induced HPA potentiation of glutamatergic toxicity on hippocampal neurons which produces atrophy and death of stress-vulnerable CA3 pyramidal neurons [44,45]. My major focus here is not shrinkage of hippocampal volume, per se, which may or may not be substantiated by future research, but rather stress-induced atrophy of neurons and loss of dendritic sprouting, which is well established in animal research. Given these findings in animals, and given the possibility that extreme stress may also produce hippocampal damage in humans, it seems reasonable to consider how this might be addressed pharmacologically.

With this as the context, it is very exciting to consider recent findings suggesting that antidepressant medications can reverse the atrophy of hippocampal neurons and increase cell survival and function. A key to antidepressant-induced neurogenesis may involve activation of Brain Derived Neurotrophic Factor (BDNF) through enhanced adrenergic and serotonergic signal transduction [46,47]. It is possible that all clinically active classes of antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs and others) produce upregulation of BDNF and, therefore, promote significant neurogenesis. As noted previously, one gateway to neurogenesis may be through post-synaptic 5-HT_{1A} receptors [34].

In addition to BDNF-mediated neurogenesis, it is important to consider another growth-promoting peptide, insulin-like growth factor 1 (IGF-1), that has been shown to promote brain metabolism, neural transmission, and neural growth and differentiation [48,49]. Because IGF-1 is suppressed by enhanced HPA activity, it is possible that a PTSD-related deficiency of

IGF-1 may also contribute to hippocampal neuronal atrophy or loss of dendrites. In short, the emerging clinical pharmacology of neurogenesis may have direct relevance to future treatment of chronic PTSD.

Perhaps a brief disclaimer or point of clarification is in order at this juncture. There remain many questions about PTSD-related abnormalities (such as the possibility of damage or atrophy of hippocampal neurons), and even more questions about the utility or potential effectiveness of treatments that promote neurogenesis to reverse such abnormalities. Therefore, it is certainly not suggested here that current scientific evidence provides a sufficient rationale for clinicians to prescribe such agents (to promote neurogenesis) in chronic PTSD. It is suggested, however, that the data are sufficiently compelling and potentially of such great theoretical and clinical importance that the time has come to conduct clinical trials addressing this possibility.

Summary

I have presented two complementary lines of speculation in this article. First, I have presented a public health model of resilience, prevention, acute intervention, and tertiary treatment to inform a pharmacotherapeutic strategy for PTSD in the future.

Second, I have proposed a rational rather than an empirical approach to the clinical pharmacology of PTSD. Such an approach suggests that efforts be directed toward the development and testing of new classes of drugs designed to target the unique pathophysiology of PTSD.

New medications for post-traumatic stress disorder

Corticotropin releasing factor antagonists
Neuropeptide Y agonists
Anti-adrenergic agents (old medications—never tested)
Selective serotonergic agents (e.g., 5-HT_{1A} agonists)
Selective opioid agents
Substance P antagonists
N-methyl-D-aspartate (NMDA)/nonNMDA/metabotropic glutamatergic modulators
Anticonvulsants (anti-kindling/sensitization agents)
Brain Derived Neurotrophic Factor promoters (antidepressants)
Insulin-like growth factor-1 agonists

It seems to me that we will be more likely to achieve clinical success in the future if we place less emphasis on the testing of already established antidepressants, anxiolytics, and anticonvulsants. Instead, I propose that we adopt

a more proactive clinical approach and focus primarily on medications that have better psychobiological specificity with respect to PTSD.

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